UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,297	06/28/2004	Rick V. Hay	28927.0009	2642

30827 7590 04/30/2007

MCKENNA LONG & ALDRIDGE LLP
1900 K STREET, NW
WASHINGTON, DC 20006

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,297	HAY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *96,100,104-106,116 and 120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/15/05;02/08/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,4,6,7,9,12-19,21-25,31,32,35-39,45-47,49-52,58-60,65,66,70-72,76,80,84,88,92,96,100,104-106,116,120,124 and 125.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 in the reply filed on 03/25/07 is acknowledged.

Accordingly, Group I, claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are examined in the instant application.

Objection

1. Claims 19, 21-25, 31-32, 35-39, 92 are objected to for the use of the abbreviated language "MRI" in claims 19, 37, 92. A full name of "MRI" is suggested.

2. Claims 19, 21-25, 31-32, 35-39 are objected to for the use of the abbreviated language "PET" in claims 19. A full name of "PET" is suggested.

Specification

1. The use of the trademarks, for example on pages 25-26, 31, 32, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are indefinite, for the recitation of the language " a derivative" in claims 1, 4,6, 7, 9, 12, 13, 15, 21, 45, 58, 65. It is not clear what constitutes "a derivative" of an antibody.

2. Claims 4, 6 are indefinite for the use of the language "biological or structural characteristics". It is not clear what "biological or structural characteristics" are referred to.

3. Claim 6 is indefinite for the use of the language "corresponding regions or sites". It is not clear how the regions or sites "correspond" with those of the monoclonal antibody of claim 1.

4. Claims 6, 7, 12, 17, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92 are indefinite for the use of the language "Met", to describe the protein of the claimed invention. This language is confusing, because "Met" is also an abbreviation of the amino acid Methionine.

Claim Rejections - 35 USC § 112, First Paragraph, Deposit

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A deposit of the hybridoma cell lines Accession Nos: PTA-4349 and PTA-4477, PTA-3414, PTA-3416, PTA-3413, and PTA-3412 is required to enable the invention of claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125. Because it is not clear that cell lines possessing the identical structure and functional properties of the hybridoma cell lines Accession Nos: PTA-4349 and PTA-4477, PTA-3414, PTA-3416, PTA-3413, and PTA-3412 are known and/or publicly available or can be reproducibly isolated without undue experimentation, a suitable deposit for patent purposes is required. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed cell lines which produce chemically and functionally distinct antibodies is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen

specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequence to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementary determining regions, can be folded to form similar binding contours, which result in similar immunochemical characteristics (William E. Paul, ed. 3rd ed. 1993, Fundamental Immunology, p. 242). The claimed cell lines are distinct and unique cell lines which produce specific antibodies, having unique properties, one of ordinary skill in the art would be forced into undue experimentation in order to make the claimed cell lines in view of the lack of exemplary materials and in view of the unpredictability associated with obtaining the exact species repeatedly. A deposit of the claimed cell lines would satisfy the requirements of 35 USC 112 first paragraph in this case. See CFR 1.801-CFR 1.809.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements. Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. Further, if a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the desposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. In

addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. Applicant's provision of these assurances would obviate this objection/rejection.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that Met, the protein product of the c-met-protooncogene, is a receptor protein tyrosine kinase (p.2, lines 13-16). The specification discloses that the extracellular domain of this receptor binds to the ligand hepatocyte growth factor/scatter factor (HGF) (p.2, lines 17-19). The specification discloses that the claimed monoclonal antibody binds to the extracellular domain of Met (table 1 on page 24). The specification, however, **does not disclose** the specific **structure of the epitope** of the claimed monoclonal antibody, for example the specific extracellular domain of the Met protein identified by a specific **sequence identification number**. That is, it is not clear that the epitope of the claimed monoclonal antibody is the extracellular domain of **which of variant Met** protein, because the specification

does not disclosure the extracellular domain of a specific Met protein identified by a sequence identification number, and because Met protein encompasses a genus of variant Met with different or unknown structure.

The prior art discloses the structure of Met and its C-terminal truncated forms (see Prat et al, 1991, Mol Cell Biol, 11(12): 5954-5962, IDS of 02/15/05). Although the prior art discloses Met and its C-terminal truncated forms (see Prat et al, 1991, Mol Cell Biol, 11(12): 5954-5962, IDS of 02/15/05), they are not representative species of the claimed genus of Met variants, in view that there is no disclosure in the specification or in the art common structure of the claimed genus of Met variants, which structure contributes to the function of Met protein. Further, there is no disclosure in the art the structure of HGF variants.

1) A "derivative" of a monoclonal antibody produced by the hybridoma cell line deposited in the American Type Culture Collection under Accession Number PTA-4349, or PTA-4477, or a "derivative" for an HGF-specific antibody encompasses an antibody with unknown structure and function.

2) Further, in view of a lack of a disclosure of the specific **structure of the epitope** of the claimed monoclonal antibody, and in view that Met protein encompasses a genus of variant Met with different or unknown structure, claims 6, 7, 12-14, 17-18, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92 encompass a monoclonal antibody specific for **a genus of variant Met** proteins, with unknown structure and function. Claims 45-47, 49-52, 58-60, 65 encompass a monoclonal antibody for treating a tumor expressing a genus of variant Met protein. Claims 66, 70-72, 80, 84, 88 and 92 encompass a method for detecting the presence of a genus of variant Met protein, using the claimed monoclonal antibody. Similarly, in view that the specific structure

of the epitope of the antibody to "HGF" is not disclosed, claims 13, 14 encompass an antibody specific for **a genus of variant HGF** proteins, with unknown structure and function.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the

genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe an antibody derivative, Met protein, or HGF protein in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide sufficient structure or common structure, to support the broad breath of the claimed genus. Nor is there any functional characteristics coupled with a known or disclosed correlation between structure and function.

The specification also fails to describe an antibody derivative, Met protein, or HGF protein, by the standards shown in the example in Lilly. The specification fails to describe a

"representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Further, the following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

In the instant application, the specification does not fully describe the genus of Met antigen, or the genus of HGF antigen. Since the instant application does not fully describe the genus of antigen to which the claimed monoclonal antibody binds, the instant application cannot claim the genus form of monoclonal antibody. Thus the specification fails to describe the claimed monoclonal antibody, by the test set out in the example of Noelle.

The specification does not provide an adequate written description of an antibody derivative, Met protein, or HGF protein that is required to practice the claimed invention. Thus, the specification does not meet the 112, first paragraph written description requirement, and one of skill in the art would reasonably conclude that Applicant did not have possession of an antibody derivative, Met protein, or HGF protein at the time the invention was made. Since the specification fails to adequately describe the product for use in the claimed method of claims 66, 70-72, 76, 80, 84, 88, 90, 92, it also fails to adequately describe the claimed method.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

1. Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are rejected under 35 U.S.C. 112, first paragraph for incorporation of **essential material** in the specification only by reference to a foreign application or patent, or to a publication.

It is noted that Met and HGF proteins are essential material for the claimed composition and method. However, the specification only refers of published references to describe Met and HGF proteins (see references on pages 2, and 41 of the instant specification). MPEP 608.01 teaches that incorporation of **essential material** in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference (see 37 CRF 1.57). The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) (see MPEP 6.19 and 6.19.01) . In other words, Applicant is required to submit a paper copy and a computer readable form copy of the Met and HGF sequences cited in the published reference as referred to in the specification, and a statement that the content of the paper and computer readable copies are the same, and include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). Applicant is also required to submit an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application.

2. Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 are also rejected under 35 U.S.C. 112, first paragraph, for lack of enablement for 1) a **derivative** of a monoclonal antibody, 2) a monoclonal antibody specific for a **genus of Met variant**, or a **genus of HGF variant**, a monoclonal useful for treating tumor

expressing a genus of Met variant, or 3) a method for detecting the presence of a genus of Met variant using the claimed monoclonal antibody.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses making monoclonal antibodies Met3 and Met 5, produced by the hybridoma cell lines PTA-4349, and PTA-4477, respectively, which are specific for the extracellular domain of the Met protein (table 1 on page 24). The specification however **does not disclose** the specific **structure of the epitope** of the claimed monoclonal antibody, for example the specific extracellular domain of the Met protein identified by a specific **sequence identification number**, supra.

Claims 1, 4, 6, 7, 9, 12-19, 21-25, 31-32, 35-39, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92, 124-125 encompass a derivative of an antibody, and a method for detecting Met using said derivative. Claims 6, 7, 12-14, 17-18, 45-47, 49-52, 58-60, 65-66, 70-72, 76, 80, 84, 88, 92 encompass a monoclonal antibody specific for **a genus of variant Met** proteins, with unknown structure and function. Claims 45-47, 49-52, 58-60, 65 encompass a monoclonal

antibody for treating a tumor expressing a genus of variant Met protein. Claims 66, 70-72, 80, 84, 88 and 92 encompass a method for **detecting** the presence of a genus of variant Met protein, using the claimed monoclonal antibody. Claims 13, 14 encompass an antibody specific for **a genus of variant HGF** proteins, with unknown structure and function.

One would not know how to make and use the claimed derivative, because the structure and function the claimed derivative cannot be predicted.

Further, one would not know how to use the claimed monoclonal antibodies specific for a **genus** of **variant** Met or variant HGF proteins, because one cannot predict that the claimed monoclonal antibody could be successfully used for detecting or treating cancer, in view that the expression of the variant Met or HGF proteins in cancer tissue, to which the claimed monoclonal antibody bind, is not predictable. It is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type. For example, Schmid S et al, 2001 (J comparative Neurology, 430(2): 160-71), teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996 (Mol Brain Res, 42: 1-17), teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2). Thus in view of the teaching in the art one cannot predict that the variant Met or HGF proteins

would express or overexpress in cancer tissue as compared to normal control tissue, and therefore, one cannot predict that the claimed monoclonal antibodies could be successfully used for detecting cancer.

3. Claims 45-47, 49-52, 58-60, 65 are also rejected under 112, first paragraph, because one cannot predict that the claimed monoclonal could be used for **treating** cancer.

The specification discloses that monoclonal antibodies Met3 and Met 5 are effective in imaging human nasopharyngeal and renal cell carcinoma xenografts in nude mice (Example 5 on p.53-54). The specification discloses that it is known in the art that the levels of Met-HGF expression is higher in breast carcinoma as compared to normal tissue, and that aberrant Met is also found in prostate carcinoma (p.2-3). The specification discloses that a number of publications disclose that anti-Met antibodies, which are antagonists to the growth factor HGF receptor, could be used for treating cancer (p.4, last two paragraph). The specification, however, does not have any data or objective evidence that the monoclonal antibodies Met3 and Met 5 have the same properties as the anti-Met antibodies disclosed in the art, and are antagonists of the HGF receptor. The specification contemplates treating a Met-expressing tumor using the claimed antibodies (p.10, last paragraph, bridging p.11, p.38-39). The specification, however, does not have any data or objective evidence that the claimed monoclonal antibody Met3 or Met5 could be successfully used for treating cancer.

One cannot predict that the claimed monoclonal antibody, including Met3 or Met5 monoclonal antibody, could be successfully used for **treating** cancer, in view that cancer immunotherapy is unpredictable. White et al, 2001 (Ann Rev Med, 52: 125-145), teach that for a successful immunotherapy, besides the specificity of the antigen, other following properties of

the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Furthermore, cancer tolerance is a well known phenomenon. Boon, 1992 (Adv Can Res, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.194-198, 203-204). Kirkin et al, 1998, APMIS, 106 : 665-679, teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and in particular peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity (p.666, second column, second paragraph, last 6 lines). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell, 1995 (J. NIH Res, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant

to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler, 1995 (Cancer Biotherapy, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Further, although the specification discloses that a number of publications disclose that anti-Met antibodies, which are antagonists to the growth factor HGF receptor, could be used for treating cancer, there is no indication that the claimed monoclonal antibody Met3 or Met5 have the same properties as the anti-Met antibodies disclosed in the art, and are antagonist antibodies, that could inhibit the action of the growth factor HGF receptor. It is noted that not any antibodies to a receptor or a protein are antagonist antibodies.

4. Claim 65 is also rejected under 112, first paragraph, because one cannot predict that the claimed monoclonal antibody could be used for **prognosing cancer.**

One cannot predict that the claimed monoclonal antibody, including Met3 or Met5 monoclonal antibody, could be successfully used for **prognosing** or predicting risk of cancer. The specification provides neither guidance on nor exemplification of how to correlate the claimed Met3 or Met 5 monoclonal antibody with the ability to use said monoclonal antibody for

prognosing or determining risk of cancer. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the claimed invention. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and **confirm marker predictive value in prospective population trials** (emphasis added) (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Moreover, the need to perform validation studies when characterizing putative biomarkers is also confirmed by Oesterreich, S et al, 1996 (Clin Cancer Res, 2: 1199-1206, especially p. 1205, first column, last three lines of paragraph before

last), who teach that false positive correlation can be obtained when using the univariate analysis to obtain a correlation of a marker with its prognostic value. Similarly, confirmation of prognosis ability of a marker protein is essential, in view of the teaching of Vandesompele J et al, 2003 (Oncogene, 22(3): 456-60). Vandesompele et al teach that the reported prognosis power of Id-2 expression in neuroblastoma cannot be confirmed, wherein Id-2 is assumed to be a direct target for MYCN protooncogene, the amplification of which is correlated with highly aggressive neuroblastoma .

Thus, without validation of the predictive value of the claimed monoclonal antibody in a prospective population trial, one cannot predict that the presence of the claimed monoclonal antibody would be predictive of risk of cancers. The data disclosed in the specification only indicates that an increased level of the Met protein could be used for **diagnosis** of cancer.

5. Claims 45-47, 49-52, 58-60, 65 are also rejected under 112, first paragraph, for the use of the language "tumor".

The **tumor,** as recited in claims 45-47, 49-52, 58-60, 65, encompasses any enlargement or abnormal growth, which is not necessarily cancerous, for example, cystic of the pancreas, splenic tumor or enlargement of the spleen, etc... (Stedman's medical dictionary, 25th ed, 1990, p.1652-1653).

It is not clear how one can successfully detect or treat or prognose a tumor, wherein the tumor cells are not necessarily cancerous, and are unrelated to cancer, and thus having different etiology and characteristics, and would not predictably overexpress Met protein, or response to cancer therapy.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6, 7, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Prat et al, 1991, Mol Cell Biol, 11(12): 5954-5962.

Claim 1 is drawn to: A monoclonal antibody selected from the group consisting of:

(a) a monoclonal antibody Met3 produced by the hybridoma cell line deposited in the American Type Culture Collection under Accession Number PTA-4349; and

(b) a monoclonal antibody Met5 produced by the hybridoma cell line deposited in the American Type Culture Collection under Accession Number PTA-4477, or an antigen binding fragment or "derivative" of said antibody.

Claim 4 is drawn to: A monoclonal antibody, or antigen-binding fragment or derivative thereof, that has all the identifying "biological characteristics" of the monoclonal antibody, fragment or derivative of claim 1.

Claim 6 is drawn to: A humanized monoclonal antibody specific for Met, wherein

(a) the heavy chain and/or light chain variable region of said antibody, or an antigen binding site of said variable regions, has all the identifying biological or structural characteristics of the corresponding regions or sites of the monoclonal antibody of claim 1; and

(b) substantially all the remainder of the humanized monoclonal antibody is of human origin,

or an antigen binding fragment or "derivative" of said humanized monoclonal antibody.

Claim 7 is drawn to: A human monoclonal antibody specific for Met that binds to the same epitope as the epitope to which the monoclonal antibody of claim 1 binds, or an antigen binding fragment or "derivative" of said human antibody.

Claim 9 is drawn to: A composition comprising the monoclonal antibody, fragment or derivative of claim 1.

Prat et al teach a panel of monoclonal antibodies against different epitopes of the extracellular domain of the Met receptor (abstract, p.5954, second column, item under Antibodies).

The monoclonal antibody taught by Prat et al seems to be a "derivative" of : 1) the monoclonal antibody produced by the hybridoma cell line deposited in the American Type Culture Collection under Accession Number PTA-4349, or PTA-4477, as claimed in claim 1, 2) The humanized monoclonal antibody as claimed in claim 6, or 3) The human monoclonal antibody as claimed in claim 7.

In addition, the monoclonal antibody taught by Prat et al seems to be the same as the monoclonal antibody as claimed in claim 4, having all the identifying "biological characteristics" of the monoclonal antibody of claim 1. That is, similar to the claimed monoclonal antibody, the antibody taught by Prat et al is directed against the extracellular domain of Met protein.

Although the reference does not explicitly teach that the monoclonal antibody is a derivative of the claimed monoclonal antibody produced by the hybridoma cell line having Accession Number PTA-4349, or PTA-4477, or of the claimed humanized or human antibody, or has all the identifying "biological characteristics" of the claimed monoclonal antibody produced by the hybridoma cell line having Accession Number PTA-4349, or PTA-4477, however, the claimed monoclonal antibody appears to be the same as the prior art monoclonal antibody. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those

taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
April 04, 2007

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600